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(71) Applicant *(for all designated States except US)*: **LABORATORIOS S.A.L.V.A.T., S.A.** [ES/ES]; Calle Gall, 30-36, Esplugues de Llobregat, E-08950 Barcelona (ES).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ARTALEJO ORTEGA, Beatriz** [ES/ES]; Calle Bordeus, 21, E-08029 Barcelona (ES). **BATLLORI CALBÒ, Javier** [ES/ES]; Esglesia Vella, 2, E-08100 Sant Fost de Campsentelles (ES). **FERNANDEZ GARCIA, Andrés** [ES/ES]; Calle Josep Irla, 6, E-08034 Barcelona (ES). **JULVE RUBIO, Jordi** [ES/ES]; Calle Compositor Mestres, 8, E-08758 Cervelló (ES).

(74) Agents: **RAMBELLI,Paolo** et al.; Jacobacci & Partners SpA, Corso Regio Parco, 27, I-10152 Torino (IT).

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(54) Title: LONG TERM STABLE ORAL PHARMACEUTICAL FORMULATION OF MICROGRANULES IN SUSPENSION

(57) Abstract: Pharmaceutical formulation obtainable subjecting conventional microgranules to an external seal-coating layer that avoids the penetration of liquid vehicle, and selecting a hydrophobic liquid vehicle with a viscosity high enough not to wet the microgranules. The seal-coating layer may be obtained by coating the microgranules with an aqueous suspension comprising film formers and plasticizers. The liquid vehicle is comprised of oily solvents, and viscosity agents. The formulation is presented in single dose sachets ready-to-use. This formulation enables the liquid oral administration of antiulcerous microgranules of benzimidazoles (omeprazole, lansoprazole, pantoprazole, rabeprazole), with several advantages comparing to commercially available extemporaneous suspensions. The new formulation of lansoprazole microgranules has a similar bioavailability and slightly higher stability than conventional hard gelatin capsules.

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# Long term stable oral pharmaceutical formulation of microgranules in suspension

The present invention relates to a stable oral pharmaceutical formulation (or preparation or composition) of microgranules in suspension. The invention also relates to the method of making said pharmaceutical formulation, and to a single-dose ready-to-use dosage form.

## BACKGROUND OF THE INVENTION

Oral administration is the most frequently employed administration route in therapy. Pharmaceutical formulations currently available for oral administration can be classified in two groups: solids forms (tablets, granules, capsules, etc.) and liquid forms (frequently aqueous or hydroalcoholic solutions). In general, oral administration of solid formulations is the most preferred one by patients. Nevertheless, there are situations in which oral liquid formulations are recommendable or even indispensable, for instance, those in which patients have swallowing difficulties or disorders (elderly patients, patients confined to bed, etc.), and those in which patients are unwilling to swallow (children).

There are some drugs that, for different reasons (stability, controlled release, etc.), are formulated as microgranules. Usually, microgranules are formed by superimposed layers, starting either from inert cores or from drug containing cores obtained by kneading-extrusion-espheronization. Microgranules of antiulcerous benzimidazoles, such as lansoprazole, omeprazole, pantoprazole and rabeprazole, are of particular commercial importance.

Usually, oral administration of microgranules involves the use of hard gelatin capsules, each one of them corresponding to a single dose. In the preparation of microgranules dispersed in liquid vehicles, several technical problems may be encountered, for instance those related with drug stability, swallowing and dosage. To ensure the appropriate dosage it is required that microgranules have a particle size that allow them to remain in suspension.

Microgranule suspensions for oral administration may be either extemporaneously prepared or ready-to-use (cf. e.g. US 5.296.236, US 5.405.619, US 5.510.119, WO 99/01129, US 5.670.171, and US 5.527.545).

There are situations in which microgranules are not stable enough to get a ready-to-use suspension. This occurs, for example, with microgranules of antiulcerous benzimidazoles (omeprazole, lansoprazole, pantoprazole, rabeprazole). Apparently, the only formulation of lansoprazole for oral liquid administration commercially available (Zoton® suspension, Wyeth and Takeda) is presented in sachets with dry microgranules for extemporaneous administration. The patient is told to mix the microgranules gently with water, and swallow immediately the resulting suspension without chewing.

Depending on the circumstances, and specially on the chemical properties of the active ingredient, some disadvantages may be encountered when microgranules are administered as extemporaneous liquid suspension. Among these disadvantages are the following: (a) chemical degradation of the active ingredient; (b) mechanical degradation of the microgranule; and (c) the nuisance for the patient that implies getting some water, putting it into a suitable vessel, cutting the

sachet, pouring their contents into the water, and shaking the mixture to form the suspension, also bearing in mind the possibility of an accidental pouring. Furthermore there are other disadvantages such as: (d) the risk of lack of hygiene of the vessel or lack of drinkable water (serious problem in wide zones of the Third World); and (e) the unpleasant sensation after ingestion of a suspension unsuitable from an organoleptically point of view, e.g. it is well known the so-called sand-effect when swallowing a suspension containing coarse particles.

From what is mentioned above, it is clear that there is an interest in obtaining new pharmaceutical formulations of long-term stable liquid suspensions of microgranules, as an alternative to the known pharmaceutical formulations of extemporaneous preparation of aqueous suspensions. It is also interesting that the new formulation can be presented as a single dose dosage form. It is particularly interesting to obtain new formulations for active ingredients that are unstable in aqueous medium, such as antiulcerous benzimidazoles (e.g. omeprazole, lansoprazole, pantoprazole, and rabeprazole).

## DETAILED DESCRIPTION OF THE INVENTION

An aspect of the present invention relates to a long-term stable oral pharmaceutical formulation comprising a suspension, in a suitable amount of a pharmaceutically acceptable liquid vehicle, of a therapeutically effective amount of microgranules comprising a pharmaceutically active ingredient.

Such a formulation presents the following characteristics: (i) the microgranules have an external seal-coating layer that avoids any substantial penetration of the liquid vehicle

therein, and (ii) the liquid vehicle is hydrophobic (oily and non-aqueous) and has a viscosity high enough not to wet substantially the microgranules. The seal-coating decreases the final porosity of microgranules and helps in increasing their stability against external agents action, among them the mentioned administration liquid vehicle.

In general, the microgranules of the formulation of the present invention may be obtained by adding an external seal-coating final step to the manufacturing of any of the microgranules conventionally used and administered either in hard gelatin capsules, or as an extemporaneous aqueous suspension. The formulation of the present invention is especially useful for the administration of microgranules that are unstable in aqueous medium, and, in particular, for the administration of antiulcerous benzimidazoles microgranules, and specifically for the administration of lansoprazole microgranules.

In a particular embodiment of the present invention, the external seal-coating layer of the microgranules comprises at least one film former, and at least one plasticizer. Among the preferred film formers are xanthan gum, cellulosic derivatives (specially hydroxypropyl methyl cellulose, hydroxymethyl cellulose and cellulose), polyacrylic acids, methacrylic acids, and salts of the latter two acids. Among the preferred plasticizers are polyethylene glycol (specially PEG 6000), triethyl citrate, phthalic acid esters, cetyl alcohol, stearyl alcohol and decanodioic acid dibutyl ester. The seal-coating may also include conventional surfactants (sodium lauryl sulfate, polysorbates, etc.), conventional opacifier pigments (e.g. titanium dioxide) and conventional lubricants (e.g.: talc, magnesium stearate).

In another particular embodiment of the present invention,

the liquid vehicle of the formulation comprises at least one oily solvent, and at least one viscosity agent, being possible that a single component shows both functions simultaneously. Among oily solvents, triisostearine esters, peanut oil, soybean oil, corn oil, and short- or medium-chain triglycerides (preferably of caprylic acid, capric acid o their mixtures) are preferred. It is convenient the water content of the oily solvent to be less than 0.5 %. Among viscosity agents, cellulosic derivatives, macrogolglycerides, polyvinylpolypyrrolidones, colloidal silica, lecithin, glyceryl monostearate, alginic acid, and derivatives of the latter are preferred. Non aqueous cosolvents such as glycerin and polyethylene glycol can be added. All liquid vehicle components are non aqueous and contribute as far as possible to the function of suspending microgranules and provide viscosity to the formulation.

The combined action of oily solvents (that do not adhere to the mucosa of superior digestive tract) and viscosity agents (that provide appropriated rheological characteristics to carry microgranules) makes possible that the liquid vehicle of the formulation of the present invention results surprisingly effective for a rapid and clean administration, with none of the inconveniences of the microgranules, minimizing sand-effect and unpleasant sensations for the patient when swallowing.

In a preferred embodiment of the present invention, with the aim of improving even more the organoleptical characteristics of the formulation, one or several additional components selected from sweeteners (e.g.: saccharose, sodium cyclamate, ammonium glycyrrhizinates, sodium saccharin, aspartame, potassium acesulfame), flavorings, pigments (e.g. titanium dioxide), surfactants (e.g.: polysorbate 80, sodium lauryl sulfate, etc.) and conventional preservatives (e.g.,

parahydroxybenzoic acid or sorbic acid) may be added to the liquid vehicle.

In another preferred embodiment of the present invention, the formulation comprises as the active ingredient an antiulcerous benzimidazole (e.g. omeprazole, lansoprazole, pantoprazole, rabeprazole).

In a still more preferred embodiment of the present invention, the formulation comprises as the active ingredient lansoprazole.

According to another aspect of the present invention, there is provided a process for the preparation of a formulation, comprising the following steps: (i) providing an external seal-coating layer to the corresponding conventional microgranules not sealed yet, by the application to said microgranules of the seal-coating layer components as an aqueous suspension; (ii) drying the microgranules so obtained; and (iii) suspending the dry microgranules in the liquid vehicle, previously prepared by mixture of their components.

In the particular embodiment of the present invention in which the conventional microgranules comprise an antiulcerous benzimidazole (omeprazole, lansoprazole, pantoprazole, rabeprazole) as active ingredient, the last layer of the conventional microgranule is an enteric layer (gastroresistant).

The step of providing a seal-coating to the conventional microgranules not sealed yet (i.e., with an enteric coating as the most external layer in the case of antiulcerous benzimidazoles) can be carried out in the same equipment used to prepare the microgranules.

According to another aspect of the present invention, there is provided a ready-to-use dosage form comprising a single dose of the formulation inside one sachet. The patient simply has to cut the upper side of the sachet and pour their contents in their mouth pushing it out from the closed end. The advantages with regard to the known sachets for extemporaneous preparation are many, as mentioned before.

Another aspect of the present invention relates to a process for the preparation of said dosage form comprising the following steps: (i) introducing in an open sachet the amount of liquid vehicle corresponding to a single dose; (ii) adding to the sachet the amount of sealed coated microgranules corresponding to a single dose; and (iii) hermetically sealing the sachet by means of pharmaceutically acceptable technology.

As shown in Table 1, liquid formulation of the present invention comprising lansoprazole microgranules has a bioavailability (measured as dissolution rate) similar to that of conventional microgranule containing hard-gelatin capsules. Surprisingly, and as shown in Tables 2 and 3, the stability of the active ingredient (measured by the amount of impurities formed over time) is even greater in the formulation of the present invention, which represents an additional advantage.

Throughout the description and claims the word "comprise" and variations of the word, such as "comprising", is not intended to exclude other additives, components, integers or steps. The terms "active ingredient", and "drug" are used interchangeably herein and refer to an agent, drug, compound, composition of matter or mixture thereof that provides some pharmacological effect. The disclosures in the abstract accompanying this application and in the application from

which priority is claimed, are incorporated herein as reference.

Additional objects, advantages and novel features of the invention will be set forth in part in the description, and in part will become apparent to those skilled in the art upon examination of the description or may be learned by practice of the invention. The following examples are provided by way of illustration, and are not intended to be limiting of the present invention.

EXAMPLES

Example 1

Oily vehicle. An oily vehicle was obtained by mixing of the ingredients mentioned below. Said oily vehicle proved useful to prepare oily suspensions of sealed microgranules of lansoprazole.

| | |
|---|---|
| Lauroyl macrogol-32 glycerides (cosolvent, viscosity agent) 4.0 % | |
| Ammonium glycyrrhizinate | 0.5% |
| Sodium saccharin | 0.1% |
| Sodium cyclamate | 2.0% |
| Flavoring | 1.0% |
| Medium-chain triglycerides, Estasan ® 3575 | q.s. to 100% |

Example 2: Oily vehicle

An oily vehicle was obtained by mixing of the ingredients mentioned below. Said oily vehicle proved useful to prepare oily suspensions of sealed microgranules of lansoprazole.

| | |
|---|---|
| Peanut oil (viscosity agent and cosolvent) | 8.0% |
| Lauroyl macrogol-32 glycerides (viscosity agent and cosolvent) | 6.0% |
| Sodium saccharin | 0.1% |
| Aspartame | 0.1% |
| Flavoring | 1.0% |
| Medium-chain triglycerides, Estasan ® 3575 | q.s. to 100% |

Example 3: Oily vehicle

An oily vehicle was obtained by mixing of the ingredients mentioned below. Said oily vehicle proved useful to prepare oily suspensions of sealed microgranules of lansoprazole.

| | |
|---|---|
| Colloidal silica (viscosity agent) | 5.0% |
| Sodium saccharin | 0.1% |
| Aspartame | 0.1% |
| Titanium dioxide | 0.5% |
| Flavoring | 1.5% |
| Medium-chain triglycerides, Estasan ® 3575 | q.s. to 100% |

Example 4: Oily vehicle

An oily vehicle was obtained by mixing of the ingredients mentioned below. Said oily vehicle proved useful to prepare oily suspensions of sealed microgranules of lansoprazole.

| | |
|---|---|
| Colloidal silica (viscosity agent) | 4.5% |
| Lauroyl macrogol-32 glycerides (cosolvent, viscosity agent) | 5.0% |
| Polysorbate 80 | 15.0% |
| Flavoring | 0.8% |
| Soybean oil | q.s. to 100% |

Example 5: oily vehicle

An oily vehicle was obtained by mixing of the ingredients mentioned below. Said oily vehicle proved useful to prepare oily suspensions of sealed microgranules of lansoprazole.

| | |
|---|---|
| Colloidal silica (viscosity agent) | 4.5% |
| Lauroyl macrogol-32 glycerides (cosolvent, viscosity agent) | 5.0% |
| Polysorbate 80 | 15.0% |
| Sodium saccharin | 0.1% |
| Flavoring | 1.0% |
| Corn oil | q.s. to 100% |

Example 6: Seal-coating

Conventional microgranules of lansoprazole, prepared from inert cores and used in conventional hard gelatin capsules, were subjected to an additional seal-coating with a suspension having the following composition:

| | |
|---|---|
| Hydroxypropyl methylcellulose (film former) | 10.0% |
| Polyethylene glycol 6000 (plasticizer) | 5.0% |
| Purified water | q.s. to 100% |

Example 7: Seal-coating

Conventional microgranules of lansoprazole, prepared from inert cores and used in conventional hard gelatin capsules, were subjected to an additional seal-coating with a suspension having the following composition:

Butylmethacrylate-(2-dimethylaminoethyl)methacrylate

| | |
|---|---|
| -methylmethacrylate copolymer, Eudragit® EPO (film former) | 10.0% |
| Dibutyl decanedioate (plasticizer and lubricant) | 5.0% |
| Stearic acid (plasticizer and lubricant) | 1.5% |
| Sodium lauryl sulfate (surfactant) | 1.0% |
| Magnesium stearate (lubricant) | 3.5% |
| Purified water | q.s. to 100% |

Example 8: Seal-coating

Conventional microgranules of lansoprazole, prepared from inert cores and used in conventional hard gelatin capsules, were subjected to an additional seal-coating with a suspension having the following composition:

| | |
|---|---|
| Hydroxypropyl methylcellulose (film former) | 10.0% |
| Cellulose (film former) | 3.0% |
| Stearic acid (plasticizer and lubricant) | 2.0% |
| Purified water | q.s. to 100% |

Example 9: Dosage in single-dose sachets of a preferred formulation

The oily suspension according to the present invention (microgranules sealed according to example 4 suspended in the oily vehicle of the example 3) was packaged in single-dose sachets. The sachets were formed of a heat-sealable complex of paper, aluminum and polyethylene. The size of said sachets (3.5 x 9.0 cm) was designed to allow their contents to be poured in the mouth, squeezing from the closed end. The packaging of the oily suspension was carried out in an automated way, but keeping the two main components of the suspension (oily vehicle and sealed microgranules) in two separate hoppers. The packaging using two different hoppers

ensures and guarantees the weight of sealed microgranules and subsequently the dosage of the active ingredient.

Example 10: In vitro release active test of one ingredient

An in vitro dissolution test for suspensions was carried out to evaluate the differences between different formulations. In vitro release control was carried out in a dissolution apparatus equipped with paddles at 50 r.p.m. The samples to be studied were placed in Teflon discs.

Table 1 illustrates the percentage of lansoprazole dissolved versus time for an oily suspension of the sealed microgranules according to example 6 in the oily vehicle of the example 4. Dissolution media employed were the following:

Acid medium (pH = 1.2)

| | |
|---|---|
| Sodium chloride | 2.0 g |
| Hydrochloric acid | 7.0 mL |
| Purified water | 1 L |

Buffer medium (pH = 6.8).

| | |
|---|---|
| Potassium phosphate | 6.84 g |
| Sodium hydroxide | 0.9 g |
| Polysorbate 80 | 2.0 g |
| Purified water | 1 L |

The determination of the released active ingredient in the different sampled times, was performed by UV spectrophotometry according to known methods.

Table 1: Percentage of dissolved lansoprazole vs. time.

| Time (min) | Oily suspension |
|---|---|
| 0 | 0 |
| 5 | 3.78 % |
| 7 | 9.88 % |
| 10 | 19.24 % |
| 15 | 33.66 % |
| 30 | 58.84 % |
| 60 | 79.18 % |

Example 11: Comparative study of the stability of the active ingredient

In a comparative study of the amount of impurities formed from comparable amounts of the active ingredient lansoprazole, in one case in form of conventional microgranules contained in hard gelatin capsules, and in the other case in form of a suspension according to the present invention (sealed microgranules according to example 6 suspended in the vehicle of example 3), surprisingly a significant lower degradation of the active ingredient was observed (lower percentage of impurities) in the case of the formulation of the present invention. Tables 2 and 3 illustrate the analytical results obtained with samples of the both aforementioned pharmaceutical forms, subjected at 40 °C and a 75 % of relative humidity, for three months.

Table 2: Percentage of certain typical impurities from the degradation of lansoprazole vs. time, in an oily suspension described in the present invention (n.d. = non detectable).

| T (month) | Sulphone derivative | N-oxide derivative | Sulfide derivative | Other impurities | Sum of all |
|---|---|---|---|---|---|
| 0 | < 0.1 % | n.d. | n.d. | < 0.1 % | 0.11 % |
| 1 | < 0.1 % | n.d. | n.d. | 0.14 % | 0.19 % |
| 2 | < 0.1 % | n.d. | n.d. | 0.15 % | 0.20 % |
| 3 | < 0.1 % | n.d. | n.d. | 0.16 % | 0.19 % |

Table 3: Percentage of certain typical impurities from the degradation of lansoprazole vs. time, in conventional microgranules contained in conventional hard gelatin capsules (n.d. = non detectable).

| T (month) | Sulphone derivative | N-oxide derivative | Sulfide derivative | Other impurities | Sum of all |
|---|---|---|---|---|---|
| 0 | < 0.1 % | n.d. | n.d. | < 0.1 % | 0.10 % |
| 1 | < 0.1 % | n.d. | < 0.1 % | 0.24 % | 0.33 % |
| 2 | < 0.1 % | n.d. | < 0.1 % | 0.40 % | 0.50 % |
| 3 | < 0.1 % | n.d. | < 0.1 % | 0.54 % | 0.65 % |

CLAIMS

1. A pharmaceutical formulation, oral and stable, comprising a suspension, in an suitable amount of a pharmaceutically acceptable liquid vehicle, of a therapeutically effective amount of microgranules comprising a pharmaceutically active ingredient, characterized in that:

(i) the microgranules have an external seal-coating layer that avoids any substantial penetration of the liquid vehicle therein, and

(ii) the liquid vehicle is hydrophobic and has a viscosity high enough not to wet substantially the microgranules.

2. The formulation according to claim 1, wherein said external seal-coating layer comprises at least one film former, and at least one plasticizer.

3. The formulation according to claim 2, wherein said film former is selected from the group consisting of xanthan gum, cellulosic derivatives, polyacrylic acids, methacrylic acids, and salts of the latter two acids.

4. The formulation according to claim 1, wherein the external seal-coating layer comprises at least one of the following pharmaceutical excipients: conventional surfactants, conventional opacifier pigments and conventional lubricants.

5. The formulation according to claim 2, wherein said plasticizer is selected from the group consisting of polyethylene glycol, triethyl citrate, phthalic acid esters, cetyl alcohol, stearyl alcohol, and decanedioic acid dibutyl ester.

6. The formulation according to claim 1, wherein said liquid vehicle comprises at least one oily solvent, and at least one viscosity agent, being possible that a single component shows both functions simultaneously.

7. The formulation according to claim 6, wherein said oily solvents are selected from the group consisting of medium- or short-chain triglycerides, triisostearine ester, peanut oil, soybean oil, and corn oil.

8. The formulation according to claim 6, wherein said viscosity agent is selected from the group consisting of cellulosic derivatives, macrogolglycerides, polyvinylpyrrolidones, colloidal silica, lecithin, glyceryl monostearate, alginic acid, and derivatives of the latter.

9. The formulation according to claim 6, wherein said liquid vehicle further comprises at least one of the following pharmaceutical excipients: sweeteners, flavorings, pigments, surfactants and preservatives.

10. The formulation according to claim 1, wherein said microgranules comprise an antiulcerous benzimidazole as active ingredient.

11. The formulation according to claim 10, wherein said active ingredient is lansoprazole.

12. A preparation process of the formulation as defined in any of the previous claims, comprising the following steps:

(i) providing an external seal-coating layer to the corresponding conventional microgranules not sealed yet, by the application to said microgranules of the seal-coating layer components as an aqueous suspension;

(ii) drying the microgranules so obtained; and

(iii) suspending the dry microgranules in said liquid vehicle, previously prepared by mixture of their components.

13. A ready-to-use dosage form of the formulation as defined in any one of claims 1 to 11, comprising a single dose of the formulation inside one sachet.

14. A preparation process of the dosage form as defined in claim 13, comprising the following steps:

(i) introducing in an open sachet the amount of liquid vehicle corresponding to a single dose;

(ii) adding to the sachet the amount of sealed coated microgranules corresponding to a single dose; and

(iii) hermetically sealing the sachet by means of pharmaceutically acceptable technology.